is likely a result of the removal of water and the use of a volatile salt in these experiments; indeed, the free volume created by removal of solvent and salt allows the DNA to be compressed on the surface and close approach of the particles within the aggregates. Third, the aggregates with the DNA-protected nanoparticles behave as semiconductors, while films formed from citrate-stabilized particles exhibit irreversible particle fusion and metallic behavior. Finally, these results point toward the use of these materials in DNA diagnostic applications where sequence specific binding events between nanoparticles functionalized with oligonucleotides and target DNA effect the closing of a circuit and a dramatic increase in conductivity (*i.e.* from an insulator to a semiconductor) (see next example).

Example 22: Detection Of Nucleic Acid Using Gold Electrodes

A method of detecting nucleic acid using gold electrodes is illustrated diagramatically in Figure 41. A glass surface between two gold electrodes was modified with 12-mer oligonucleotides **1** (3' $NH_2(CH_2)_7O(PO^{2-})$O-ATG-CTC-AAC-TCT [SEQ ID NO:59]) complementary to target DNA **3** (5' TAC GAG TTG AGA ATC CTG AAT GCG [SEQ ID NO:60]) by the method of Guo *at al., Nucleic Acids Res.*, **22**, 5456-5465 (1994). Oligonucleotides **2** (5' $SH(CH_2)_6O(PO^{2-})$O-CGC-ATT-CAG-GAT [SEQ ID NO:50]) were prepared and attached to 13 nm gold nanoparticles as described in Examples 1 and18 to yield nanoparticles **a**. Target DNA **3** and nanoparticles **a** were added to the device. The color of the glass surface turned pink, indicating that target DNA-gold nanoparticle assemblies were formed on the glass substrate. Next, the device was immersed in 0.3 M NaCl, 10 mM phosphate buffer and heated at 40 °C for 1 hour to remove nonspecifically bound DNA, and then treated with a silver staining solution as described in Example 19 for 5 minutes. The resistance of the electrode was 67 kΩ.

For comparison, a control device modified by attaching oligonucleotides **4**, instead of oligonucleotides **1**, between the electrodes. Oligonucleotides **4** have the same sequence (5' $NH_2(CH_2)_6O(PO^{2-})$O-CGC-ATT-CAG-GAT [SEQ ID NO:50]) as oligonucleotides **2** on the nanoparticles and will bind to target DNA **3** so as to prevent binding of the nanoparticles.

The test was otherwise performed as described above. The resistance was higher than 40 MΩ, the detection limit of the multimeter that was used.

This experiment shows that only complementary target DNA strands form nanoparticle assemblies between the two electrodes of the device, and that the circuit can be completed by nanoparticle hybridization and subsequent silver staining. Therefore, complementary DNA and noncomplementary DNA can be differentiated by measuring conductivity. This format is extendable to substrate arrays (chips) with thousands of pairs of electrodes capable of testing for thousands of different nucleic acids simultaneously.